Paper No. 23

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RONALD M. EVANS, MICHAEL B. MCKEOWN, ANTHONY E. ORO, WILLIAM A. SEAGRAVES, and TSO-PANG YAO

Appeal No. 2003-1139
Application No. 09/526,298

ON BRIEF[1]

Before WILLIAM F. SMITH, McKELVEY and ADAMS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 14-19 and 35-48, which are all the claims pending in the application.

Claim 14 is illustrative of the subject matter on appeal and is reproduced below:

14. A method for modulating the expression of an exogenous gene in a subject containing:
    (i) A DNA construct encoding said exogenous gene under the control of a steroid or steroid-like hormone response

[1] Appellants waived their request for oral hearing. Paper No. 22. Accordingly, we considered this appeal on Brief.

element; wherein said response element is not normally present in the cells of said subject,

(ii) a receptor which is not normally present in the cells of said subject, wherein said receptor, in the presence of its associated ligand and the ultraspiracle receptor, binds to said steroid or steroid-like hormone response element, and

(iii) ultraspiracle receptor;

said method comprising administering to said subject an effective amount of said associated ligand; wherein said ligand is not normally present in the cells of said subject; and wherein said ligand is not toxic to said subject.

The references relied upon by the examiner are:

Crystal, "Transfer of Genes to Humans: Early Lessons and Obstacles to Success," Science, Vol. 270, pp. 404-410 (1995)

Orkin et al. (Orkin), "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy," pp. 1-41 (NIH, 1995)

Verma et al. (Verma), "Gene Therapy-Promises, Problems and Prospects," Nature, Vol. 389, pp. 239-242 (1997)

GROUND OF REJECTION

Claims 14-19 and 35-48 stand rejected under 35 U.S.C. § 112, first paragraph, as being based on an insufficient disclosure to enable the scope of the claimed invention.

We reverse.

BACKGROUND

Steroid and thyroid hormones are involved in eukaryotic transcriptional regulation. Specification, page 1. "The effects of hormones are mediated by interaction with specific, high affinity binding proteins referred to as receptors." Id. These receptor proteins "are capable of modulating specific gene expression

in response to hormone stimulation by binding directly to cis-acting elements." Specification, page 2. Specifically, steroid or thyroid hormones

> enter cells and bind to the corresponding specific receptor protein, initiating an allosteric alteration of the protein. As a result of this alteration, the complex of receptor and hormone ... is capable of binding with high affinity to certain specific sites on chromatin. One of the primary effects of steroid and thyroid hormones is an increase in transcription of a subset of genes in specific cell types.

Id. DNA binding studies have demonstrated that some hormone receptors, e.g., the glucocorticoid receptor and the estrogen receptor, bind to their hormone response elements as homodimeric complexes. Specification, page 3. Other studies, however, have revealed that some receptors, including the retinoic acid receptor and thyroid hormone receptor, cannot efficiently bind to their response elements as homodimers. Id. It has been found that additional nuclear factors are required for these receptors to achieve high affinity DNA binding. Id. Appellants disclose (specification page 4), that the insect derived ultraspiracle receptor can combine with various members of a first receptor, the steroid/thyroid superfamily of receptors, to form a multimeric complex receptor. Accordingly, appellants disclose (specification, bridging sentence, pages 4-5), the ultraspiracle receptor, or at least the dimerization domain of this receptor, "is capable of modulating the ability to the first receptor species to trans-activate transcription of genes maintained under steroid hormone or hormone-like expression control in the presence of cognate ligand for said first receptor."

DISCUSSION

According to the examiner (Answer, bridging paragraph, pages 3-4), the specification provides an enabling disclosure of

> methods drawn to the induction or repression of a specific gene by a member of the steroid/thyroid superfamily of receptors which associates with at least the dimerization domain of [the] ultraspiracle receptor, in the presence of ligand for said member, where the expression of said gene is maintained under the control of a hormone response element to which said member binds where the method comprises exposing the expression system to at least the dimerization domain of an ultraspiracle receptor where the method is in vitro or in cells in culture.

Notwithstanding this disclosure, the examiner finds (Answer, page 4), to the extent the scope of the claims includes "nucleic acid based therapy," the specification does not contain an enabling disclosure for the full scope of the claimed invention. While the phrase "nucleic acid based therapy" does not expressly appear in the claims (see e.g., Brief, page 9), the examiner finds (Answer, page 4), "the claims require the integration of a gene coding for an ultraspiracle receptor and/or the introduction of a construct containing the hormone response sequence where said construct would further comprise a desired exogenous gene to be regulated by the ultraspiracle receptor...." In this regard, we note that appellants disclose (specification, bridging paragraph, pages 19-20), receptors, including the ultraspiracle receptor, that are not normally present in the cells of a subject

> can be provided to said subject by direct introduction of the proteins themselves, by introduction of RNA or DNA construct(s) encoding said receptors, by introduction of cells harboring genes encoding said receptor and/or response element, and the like. This

> can be accomplished in a variety of ways, e.g., by microinjection, retroviral infection, electroporation, lipofection, and the like.

According to the examiner (Answer, bridging paragraph, pages 4-5), "the instant specification fails to teach one of skill in the art how to integrate the gene construct for the exogenous ultraspiracle receptor to specific desired cells such that expression would be at a level adequate for inducing the expression of a gene under the appropriate hormone response element."

With reference to Crystal, Verma and Orkin, the examiner argues (Answer, page 5), "[t]he art has shown that there are no routine methods and has further shown that one cannot expect positive results using methods known after the time of invention let alone what was known at the time of the instant invention." With reference to Verma, the examiner finds (Answer, page 6), "although gene therapy provides promise for the treatment of disease ... there are general obstacles faced by the artisan in the practice of gene therapy where the instant specification fails to provide adequate guidance to overcome these obstacles to practice the instant invention." According to the examiner (id.), "[t]his position is further taken in view of the disclosure of Orkin et al[.] where it is also discussed that [there are] may problems of gene therapy that need to be overcome...." The examiner also finds (id.), "Crystal reviews the state of the art of gene therapy and discusses the obstacles that still remain to effect nucleic acid based therapies and discusses the potential of nucleic acid based therapies." Based on this evidence, the examiner concludes (Answer, page 6),

> It is clear from the art that the art of gene therapy is unpredictable and the state of the art at the time of invention would require

> specific guidance for any particular gene therapy where no routine methods are known. One of skill in the art would need to overcome the basic problems addressed in the art to practice the instant invention as it relates to gene therapy.

We note that the examiner's focus in setting forth this rejection is that the field of gene therapy itself is unpredictable. The references relied upon by the examiner discuss the field of gene therapy in general and do not specifically address appellants' claimed invention. In our opinion, the examiner's concern in regard to the unpredictability of the field of gene therapy in general is misplaced. As explained by our appellate reviewing court, "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." In re Brana, 51 F.3d 1560, 1568, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). In Brana, the court observed that a claimed invention need not have entered Phase II clinical trials in order to be considered useful under the patent laws. Id., at 1568, 34 USPQ2d at 1442-1443. In other words, a claimed invention may be considered useful or enabled under the patent statutes at a time before the invention is conclusively shown to have a clinical or therapeutic effect. Viewing the references relied upon by the examiner in light of the correct legal standard; we do not find that they establish a prima facie case of lack of enablement. In this regard, we note that Crystal teaches (page 405, column 3),

> Probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible. Although gene

> transfer has not been demonstrated in all recipients, most studies have shown that genes can be transferred to humans whether the strategy is ex vivo or in vivo, and that all vector types function as intended. Taken together, the evidence is overwhelming, with successful human gene transfer having been demonstrated in 28 ex vivo and 10 in vivo studies....

To satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, a patent application must adequately disclose the claimed invention so as to enable a person skilled in the art to practice the invention at the time the application was filed without undue experimentation. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371-72, 52 USPQ2d 1129, 1136 (Fed. Cir. 1999). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In our opinion, on this record, the examiner has not shown that undue experimentation would have been required to practice the claimed method. The examiner's concerns, and the evidence cited in support of the rejection, are mainly directed to sources of unpredictability and experimentation involved in gene therapy in general, rather than the claimed method in particular.

We find no analysis on this record consistent with the Wands factors. Instead, we find only the examiner's conclusion that the field of gene therapy is unpredictable. Absent a fact-based explanation from the examiner

based upon the correct legal standard, i.e., one that does not require gene therapy being a "routine practice of medicine," we do not find that the examiner has established a prima facie case of nonenablement.

Accordingly, we reverse the rejection of claims 14-19 and 35-48 under 35 U.S.C. § 112, first paragraph.

REVERSED

William F. Smith
Administrative Patent Judge

Fred E. McKelvey
Senior Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

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